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CASE REPORTS

Sudden death in hypertrophic cardiomyopathy with normal left ventricular mass

Barry J Maron, Amy H Kragel, William C Roberts

Abstract

An active, healthy, and symptom free 16 year old boy with a family history of hypertrophic cardiomyopathy died suddenly while walking home from school. Necropsy showed absence of left ventricular hypertrophy (that is, normal heart weight), though the characteristic histological abnormalities of hypertrophic cardiomyopathy, such as cardiac muscle cell disorganisation and abnormal intramural coronary arteries, were present. It is likely that this patient had hypertrophic cardiomyopathy and died before left ventricular hypertrophy developed.

Hypertrophic cardiomyopathy is a primary myocardial disease, often inherited, in which the morphological and clinical features are diverse.[1–4] The most characteristic anatomical feature of the disease is left ventricular hypertrophy in the absence of ventricular dilatation, unassociated with another cardiac or systemic disease which itself could produce left ventricular hypertrophy.[5]

In patients with hypertrophic cardiomyopathy, however, left ventricular hypertrophy is not always fully expressed within the first two decades of life.[6] In children with this disease left ventricular hypertrophy is often progressive or develops for the first time when body growth and maturation accelerate.[1 6]

Sudden death and cardiac arrest are the most devastating consequences of hypertrophic cardiomyopathy and they are most common in youthful patients with few or no symptoms[2 7 8] and substantial left ventricular hypertrophy.[1 2 8 9] The boy with hypertrophic cardiomyopathy that we describe died suddenly before the typical gross morphological features of the disease developed.

Case report

A 16 year old boy complained of feeling unwell at the end of the school day. Shortly afterwards he collapsed while walking home. Onlookers promptly started cardiopulmonary resuscitation, but these measures were unsuccessful.

According to his mother, the boy had been active, healthy, and in generally good physical condition until the day he died. He had not been involved in competitive athletics, but had often participated in bowling and occasionally lifted weights. He used neither drugs nor alcohol. There was, however, a strong family history of cardiac disease[1] (fig 1). His mother, brother, maternal aunt, and two maternal uncles have clinically and echocardiographically confirmed hypertrophic cardiomyopathy. These relatives showed various patterns of asymmetrical left ventricular hypertrophy.[1–4] The maximum ventricular septal thickness in the relatives ranged from 17 mm to 28 mm; none had systolic anterior motion of the mitral valve. The patient's maternal grandmother died at age 42 with congestive heart failure of uncertain cause (heart weight at necropsy was 530 g).

A complete necropsy was performed. The patient was 1·70 m tall and weighed 66 kg. He

Cardiology and Pathology Branches, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA
B J Maron
A H Kragel
W C Roberts

Correspondence to
Dr Barry J Maron, National Institutes of Health, National Heart, Lung, and Blood Institute, Building 10, Room 7B15, Bethesda, MD 20892, USA.

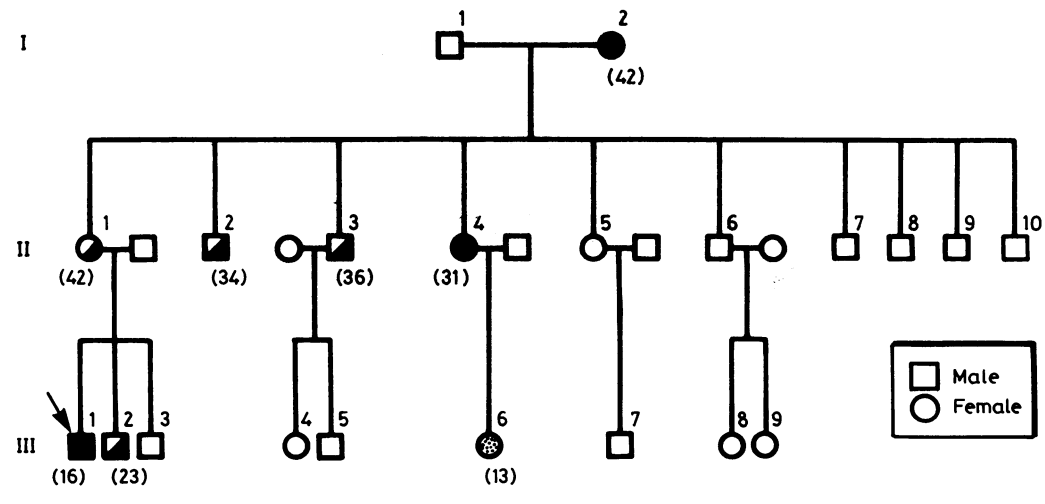

Figure 1 Pedigree of the patient (arrow) described in this report. Solid symbols indicate death from hypertrophic cardiomyopathy; those represented by half filled symbols are alive but affected by hypertrophic cardiomyopathy. Open symbols indicate that no clinical data are available. The stippled symbol represents a patient with symptoms suggestive of hypertrophic myopathy who was never investigated clinically. Ages are given in parentheses.

was well developed and well nourished. Mass spectrophotometric analysis for over 300 drugs (including volatile alcohols, narcotics, antihistamines, phenothiazines, barbiturates, synthetic narcotics, various sedatives, and cocaine) were performed on blood, urine, and lung tissue, and all were negative. All non-cardiac organs were normal.

The heart weighed 330 g and was judged to be within normal limits for sex and body size (that is $\leqslant 345$ g according to Ludwig,[10] < 380 g by the standards of Reiner,[11] and < 420 g according to Kitzman *et al*[12]). In addition, the absolute heart weight (and heart weight corrected for body weight) of the patient was the lowest among the 75 weighed specimens from male patients $\geqslant 15$ years old with hypertrophic cardiomyopathy who died of cardiac or non-cardiac causes and were studied in the Pathology Branch from 1960 to 1988 (fig 2D).

The epicardium was smooth and glistening and subepicardial adipose tissue was not increased. The ventricular and atrial chambers were non-dilated and the cardiac valves were normal (fig 2A). The thickness of the ventricular septum and left ventricular free wall did not exceed 15 mm (normal thickness $\leqslant 15$ mm) in nearly all segments of the left ventricular wall (fig 2A). Limited portions of the distal (caudal) left ventricular free wall were up to 17 or 18 mm in thickness. Thickening of these small regions of wall were believed to be postmortem changes[13] rather than segmental hypertrophy,[14] in view of the patient's overall normal heart weight. There was no grossly visible myocardial necrosis or fibrosis nor any mural endocardial plaques. The epicardial coronary arteries were widely patent without evidence of atherosclerotic plaques.

The sinoatrial and atrioventricular nodal areas were dissected, serially sectioned, and examined every 8 μm; no abnormalities of the conducting tissue or small arteries were identified. In addition, seven transverse blocks of left ventricular myocardium were obtained, including four from the proximal (cephalad), middle, and distal (caudal) regions of the ventricular septum and three from the left ventricular free wall at the same levels. Histological sections (6 μm thick) were stained with haematoxylin and eosin and by the Movat method and examined by light microscopy.

Numerous foci of disorganised cardiac muscle cells were identified in which adjacent cells or bundles of cells were arranged at oblique and perpendicular angles to one another (fig 2B).

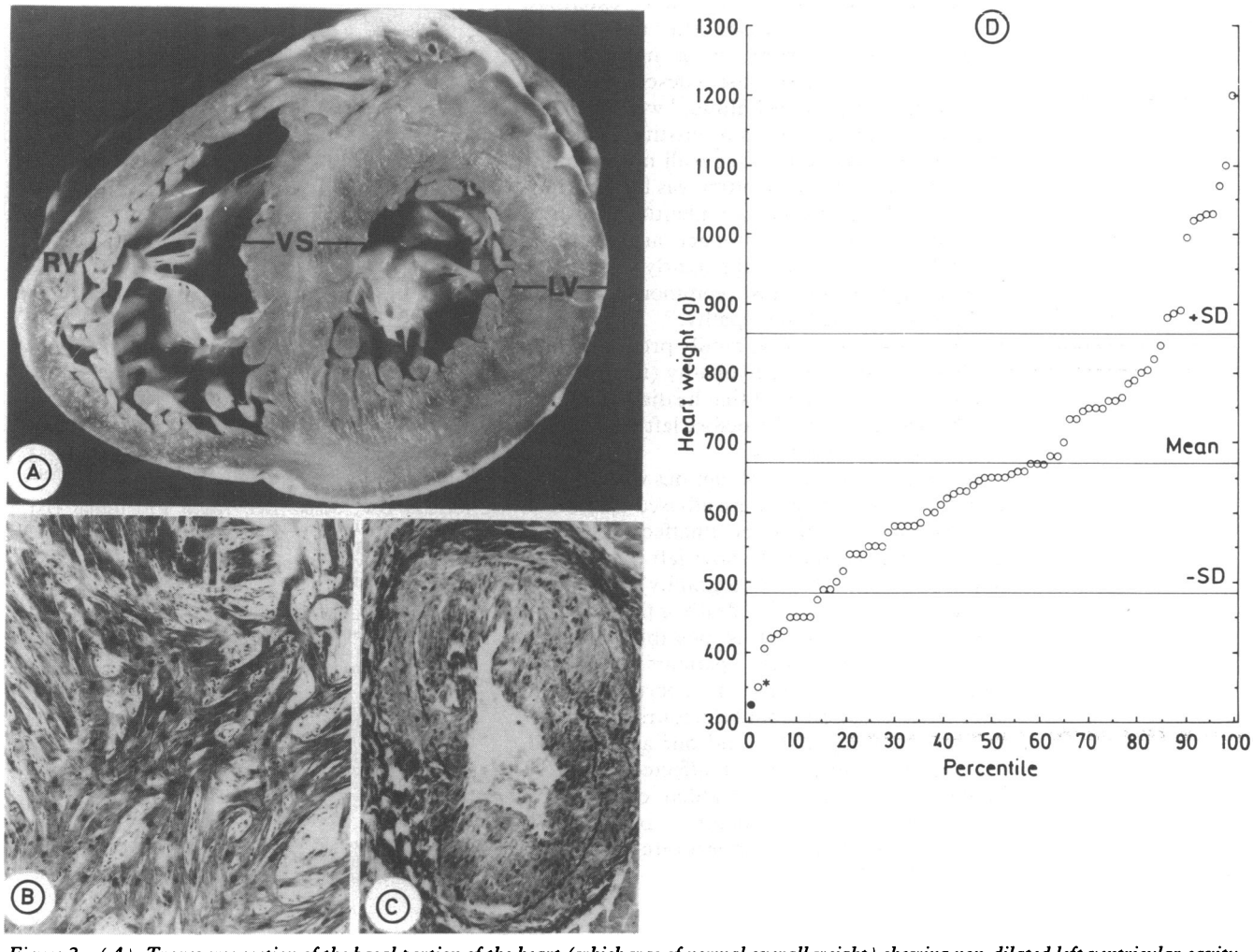

Figure 2 (A) Transverse section of the basal portion of the heart (which was of normal overall weight) showing non-dilated left ventricular cavity and normal ventricular septal (VS) and left ventricular free wall (LV) thicknesses; RV, right ventricular wall. (B) Region of cardiac muscle cell disorganisation in the left ventricular free wall, in which adjacent cells were oriented obliquely and perpendicularly. Haematoxylin and eosin stain, original magnification × 80. (C) Abnormal intramural coronary artery showing thickened wall and apparently narrowed lumen. Movat method; original magnification × 80. (D) Heart weights of 75 male patients with hypertrophic cardiomyopathy in the Pathology Branch registry. The solid symbol represents the patient reported here; the asterisk identifies the patient with the next lowest heart weight, a 49 year old man without a history of cardiac symptoms who died of renal cell carcinoma.

We measured the overall extent of cellular disorganisation from photographic enlargements of the histological sections.[14] Of the cardiac muscle cells analysed, 17% in the left ventricular free wall and 4% in the ventricular septum were judged to be disorganised. In addition, we identified eight abnormal intramural coronary arteries with thickened walls and apparently narrowed lumen[15] (five in the septum and three in the free wall) (fig 2C).

Discussion

All earlier studies of patients with hypertrophic cardiomyopathy who died suddenly (or survived a cardiac arrest) reported left ventricular hypertrophy and usually a considerable increase in left ventricular mass.[1 2 9 16] Our patient, however, did not show the gross morphological features that are typical of hypertrophic cardiomyopathy. The heart weight was within normal limits,[10-12] and there was no mitral valve thickening, mural endocardial plaque in the left ventricular outflow tract, or left atrial enlargement. Therefore, the anatomical diagnosis of hypertrophic cardiomyopathy in our patient depended on the histological findings. For example, disorganisation of cardiac muscle cells in the left ventricular myocardium was more extensive than that found in diseases other than hypertrophic cardiomyopathy or in normal controls.[14] Using a previously described morphometric mapping technique,[14] we calculated that cellular disorganisation constituted almost 20% of left ventricular free wall myocardium (while the ventricular septum was less severely affected). In addition, we identified several abnormal intramural coronary arteries with thickened walls and apparently narrowed lumens, typical of those commonly seen in hypertrophic cardiomyopathy.[15] These histological findings and the family predisposition to hypertrophic cardiomyopathy (five had the disease) strongly suggest that he died of hypertrophic cardiomyopathy before left ventricular hypertrophy developed.

At present, members of families with hypertrophic cardiomyopathy are advised that those relatives who seem to be unaffected by the disease (that is, do not show left ventricular hypertrophy on echocardiography) are not at that time at risk of sudden death or the development of symptoms. It is possible that the identification of other patients who die suddenly in the absence of hypertrophy will alter our perceptions about the course of hypertrophic cardiomyopathy and our approach to the genetic counselling of affected families. None the less cases of sudden death from hypertrophic cardiomyopathy before left ventricular hypertrophy appears are likely to be uncommon.

We cannot be certain that left ventricular hypertrophy and wall thickening would not have developed in our patient. Indeed, previous echocardiographic studies have shown that children with a genetic predisposition to hypertrophic cardiomyopathy can develop left ventricular hypertrophy for the first time during adolescence when body growth and development are accelerated.[6]

Our patient seems to be an unusual example of an individual who was genetically predisposed to develop hypertrophic cardiomyopathy and who died suddenly before left ventricular mass increased. The only structural evidence of hypertrophic cardiomyopathy at necropsy was cardiac muscle cell disorganisation and abnormal intramural coronary arteries.

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